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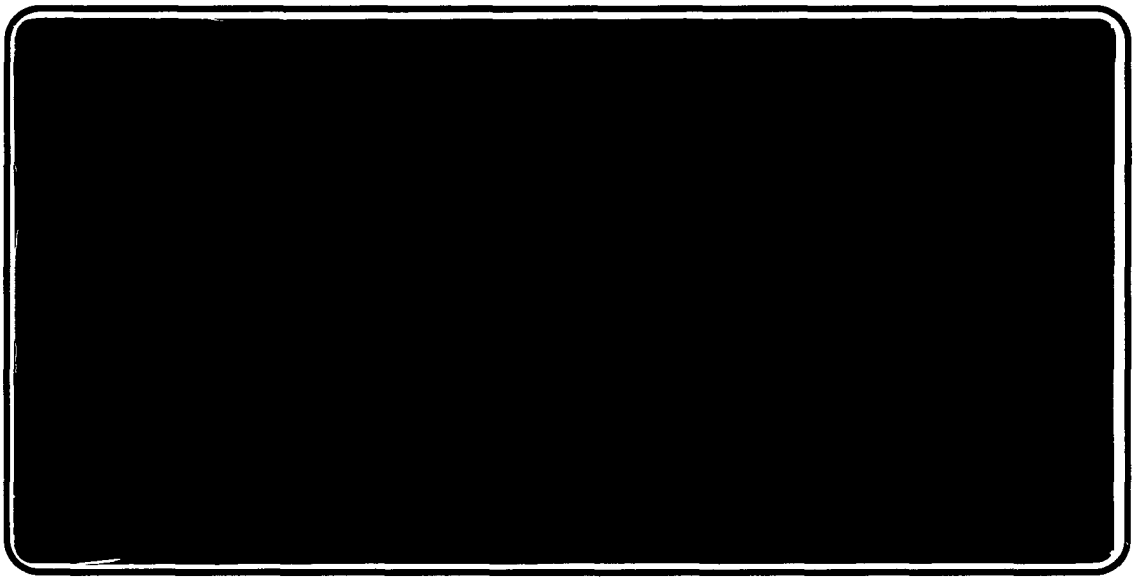

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BIOCONCENTRATION FACTORS AND LIPID SOLUBILITY

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Abstract

The relationship between bioconcentration and lipophilicity breaks down for several medium and high molecular weight solutes that bioconcentrate either to a small extent or not at all. Much of the failure is attributed to the relatively low solubility of these compounds in lipid. Correction for this effect through a term in octanol solubility leads to a general and surprisingly accurate (r=0.95) structure-bioconcentration equation.

The bioconcentration factor (BCF) in fish is frequently related to the octanol:water partition coefficient K_{ow} through

$$\log BCF = c_1 + c_2 \log K_{ow} \qquad (1)$$

where c_1 and c_2 are constants. The relationship breaks down for high K_{ow} compounds such as octachloronaphthalene which do not bioconcentrate (1), and a similar trend is reported for many dyes (2). Thus, while water solubility and other physical parameters can usually be calculated within the tolerances necessary for environmental work, BCF can only be estimated qualitatively.

Much effort (1-15) has gone into understanding why the BCF-K_{ow} relationship is "cut-off" for superlipophilic compounds (log K_{ow} >6). It has been reasoned that the breakdown originates from the inability of large compounds to pass through the gill membrane (1,5,8,10,15). In this case, a sharp difference in BCF should occur between structures on either side of the cut-off. Another view is that superlipophilics bioconcentrate less because they are relatively less soluble in lipid (4). Here, the drop in BCF with increasing size should be more gradual.

The cut-off at which the BCF levels off is actually a function of molecular shape and/or size rather than of lipophilicity. For example, low BCFs are also observed for dyes of relatively high molecular weight, but of log K_{ow} < 6 (2). Consider two solutes, one at the molecular size cut-off, and one slightly beyond it. A consequence of the lipid solubility hypothesis (4) is that γ_{lipid} must change more rapidly than γ_{water} for BCF to

decrease. This is reasonable since lipid is highly structured, and should resist the incursion of large solutes more than water does. Octanol is much less structured than water, and γ_o (o:octanol) should change less rapidly than γ_{water} for nonpolar solutes. Thus, beyond the cut-off, K_{ow} should increase with molecular size, whereas BCF should decrease.

The partition coefficient K_{ow} captures the hydrophobicity of lipid, but does not fully reflect the structure of the lipid matrix. We reasoned that combining K_{ow} with a term in γ_o, the solute activity coefficient in octanol, would be a useful refinement. Both $\gamma_{octanol}$ and γ_{lipid} should be small and relatively constant for small nonpolar solutes, and should increase with increasing solute size beyond a threshold value. Hence, a simple way to correct eq. 1 for lipid resistance would be to include a term in γ_o, or more conveniently, in octanol solubility (S_o), which gives

$$\log BCF = c_3 + c_4 \log K_{ow} + c_5 \log S_o + c_6 (mp-25) \qquad (2)$$

where c_3 - c_6 are constants, and mp is the melting point in °C. The mp term is intended to allow octanol solubilities for both liquids and solids to be included in the same equation (16). For liquids, mp is taken as 25 to remove the entire term.

BCF and associated values were collected for the compounds listed in Table I. Values for γ_o were calculated by the UNIFAC method (21). S_o values are relatively scarce; S_o-γ_o pairs could be acquired for only 18 compounds in Table I, and eq. 3

$$\log S_o = 0.762 - 0.0065\ (mp-25) - 1.19 \log \gamma_o \qquad (3)$$

$$(n=18,\ r=0.96)$$

was obtained from these values. An analogous equation has been reported (22) for water-saturated octanol. Eq. 3 was used to calculate S_o for the remaining compounds in Table I.

BCFs calculated from eq. 1 (c_1=-0.78; c_2=0.75) are compared to measured values in Figure 1; as expected, the fit is poor (r=0.74). A marked improvement occurs with eq. 2 which leads to

$$\log BCF = -1.178 + 1.04 \log K_{ow} + 0.782 \log S_o - 0.0009\ (mp-25)$$

$$(n=36,\ r=0.95) \qquad (4)$$

The relationship is illustrated in Figure 2. The fit is good even though metabolic effects are not considered, and the BCF data in Table I are uncorrected for variations in lipid content of the different species used. A disturbing feature of eq. 4 is that the coefficient of the melting point term is much lower than the expected value of 0.01. For the data considered, the mp term is statistically insignificant. We believe this to be an anomaly. Most of the compounds in Table I are solids, and there is a strong correlation (r=0.82) between log S_o and mp within the series, which lowers the mp coefficient. This effect has been observed in another application (23).

The difference in the quality of fit between Figure 1 and Figure 2 emphasizes the importance of the S_o term in eq. 4. It seems that lipid-solute incompatibility is responsible for most

of the scatter in the conventional BCF-K_{ow} relationship (Figure 1). Equation 4 should be considered as preliminary. It is based on only 18 S_o measurements, and the coefficient of the mp term is unexpectedly low as discussed above. Also, octanol-miscible liquids should probably be represented by a single value that has yet to be chosen.

Finally, we applied eq. 4 to a number of solutes known to be underestimated by eq. 1. The results are shown in Table II, and except for octachloronaphthalene, the estimates are reasonable. Opperhuizen et al. suggest (1) that this and other structures whose cross-sections exceed 9.5Å will be excluded by the gill. It follows that eq. 4 should not apply to these solutes.

In summary, we offer a simple equation that can handle most polar and nonpolar compounds that fall outside the range of the conventional BCF-K_{ow} relationship. The equation is based on the premise (4) that the structure of the lipid matrix leads to strong solute non-ideality. The accuracy of the equation is good (r=0.95), with an exception noted for octachloronaphthalene which appears to be too large to penetrate the gill (1) and falls outside the scope of eq. 4.

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Captions to Figures

Fig 1. Comparison of measured BCFs with estimates from eq 1.

Fig 2. Comparison of measured BCFs with estimates from eq 4.

Table I: Comparison of measured BCF's with values estimated from eq. 4

	mp (°C)	log P	log S_o	log BCF meas	log BCF calc	γ_o[a]
1,2-dichloroethane	liq.	1.45[b]	0.45[c]	0.30[b]	0.64	
dye IX	146	4.00[d]	-2.25[e]	0.30[e]	1.10	
atrazine	177	2.63[e]	-1.32[e]	0.48[e]	0.38	
dye II	225	3.40[d]	-3.56[e]	0.48[e]	-0.61	
dye VIII	117	4.10[e]	-2.50[e]	0.70[e]	1.04	
dye IV	219	4.40[e]	-3.34[e]	0.70[e]	0.60	
isophorone	liq.	1.67[b]	0.43[c]	0.85[b]	0.86	
dye X	173	4.50[e]	-2.23[e]	0.90[e]	1.61	
dye I	175	5.40[d]	-3.83[e]	1.00[e]	1.29	
carbon tetrachloride	liq.	2.64[b]	0.64[c]	1.24[b]	2.00	
dye VII	170	5.40[d]	-2.65[e]	1.76[e]	2.22	
hexachloroethane	192	3.93[b]	-0.35[c]	2.14[b]	2.23	
1,4-dichlorobenzene	53	3.59[f]	0.25[e]	2.33[h]	2.72	
lindane	113	3.85[b]	-1.15[c]	2.51[b]	1.88	
acenaphthene	93	3.97[b]	-0.59[g]	2.58[b]	2.42	5.11
naphthalene	81	3.59[h]	-0.02[g]	2.63[b]	2.48	3.57
biphenyl	71	3.88[h]	-0.16[g]	2.64[b]	2.68	4.58
4-chlorobiphenyl	77	4.26[b]	-0.22[g]	2.77[b]	3.02	4.55
benzyl butyl phthalate	liq.	4.05[b]	-0.59[c]	2.89[b]	2.68	
fluorene	114	4.18[g]	-0.65[g]	3.11[h]	2.57	6.21
1,2,3,5-tetrachlorobenzene	51	4.65[b]	-0.18[c]	3.26[b]	3.41	
1,2,4-trichlorobenzene	liq.	4.27[b]	0.11[c]	3.32[b]	3.16	
1,4-dichloronaphthalene	68	4.88[i]	-0.34[c]	3.36[i]	3.60	
phenanthrene	97	4.57[g]	-0.40[g]	3.42[b]	3.18	
pyrene	150	5.18[g]	-0.85[g]	3.43[h]	3.42	12.6
2-chloronaphthalene	60	4.19[i]	-0.15[c]	3.63[i]	3.55	
1,2,4,5-tetrabromobenzene	182	6.09[b]	-2.76[c]	3.81[b]	3.06	
decachlorobiphenyl	305	8.26[j]	-2.77[g]	4.02[j]	4.97	27.0
pentachlorobenzene	83	5.19[b]	-0.50[c]	4.11[b]	3.78	
hexachlorobenzene	230	6.53[f]	-1.82[e]	4.27[e]	3.98	
2,2',3,3',4,4',5,5'-octachlorobiphenyl	159	7.10[j]	-1.73[c]	4.35[j]	4.79	
1,3,7-trichloronaphthalene	113	5.59[i]	-0.71[c]	4.43[i]	3.97	
DDT	109	6.19[k]	-1.07[e]	4.47[h]	4.33	

Table I continued

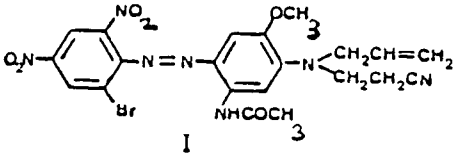
	mp (°C)	log P	log S_o	log BCF meas	log BCF calc	γ_o
1,3,5,7-tetrachloronaphthalene	180	6.38[i]	-1.20[c]	4.53[i]	4.33	
2,2',5,5'-tetachlorobiphenyl	87	6.10[j]	-0.63[g]	4.92[j]	4.63	
2,2',4,4',5,5'-hexachlorobiphenyl	103	6.90[j]	-1.19[c]	5.32[j]	5.05	
<u>additional compounds used for developing eq. 3</u>						
4,4'-dichlorobiphenyl	77[h]		-1.15			4.55
1-methyl fluorene	85[h]		-0.56			6.23
2,4,5-trichlorobiphenyl	77[h]		-0.75			6.78
anthracene	216[h]		-1.93			7.38
2,3,4,5-tetrachlorobiphenyl	91[h]		-0.86			8.43
2,3-benzofluorene	209[h]		-1.75			12.4
chrysene	255[h]		-2.70			14.6
2,3-benzanthracene	357[h]		-2.28			14.6
perylene	277[h]		-2.52			24.8
1,2,5,6-dibenzanthracene	266[h]		-3.03			27.8
coronene	360[h]		-3.41			79.4

[a]Used to develop eq. 3. [b]Obtained from ref 6. [c]Calculated with eq. 3. [d-k]Obtained from ref 17(d), 2(e), 16(f), 18(g), 19(h), 1(i), 4 (j), 20(k).

Table II: Comparison of measured BCF's of large solutes with values calculated from eq. 4.

	mp (°C)	log P	log S_o	log BCF meas	log BCF calc
octachloronaphthalene	197	7.9[a]	-1.81[b]	nd[c]	6.0
hexabromobenzene	>300	>6[d]	<-4.33[b]	nd[e]	<1.4
dye III	225	3.5[f]	-3.48[f]	<0.7[f]	-0.4
dye V	148	4.0[f]	-3.04[f]	<0.7[f]	0.6
dye VI	184	4.41[f]	-2.72[f]	<0[f]	1.1

[a]Calculated as described in ref. 22. [b]Calculated from eq. 3. [c]Little or no bioconcentration (ref 1). [d]Ref 4. [e]Little or no bioconcentration (ref 3). [f]Ref 2.



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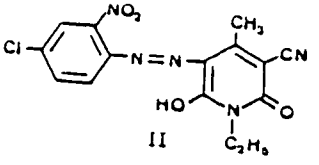

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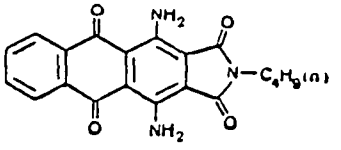

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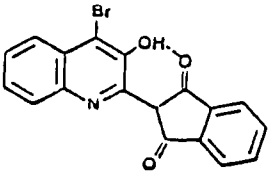

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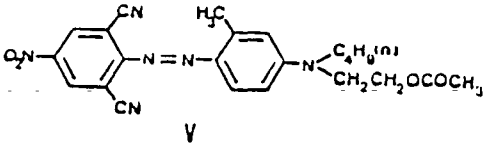

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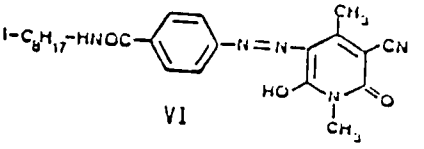

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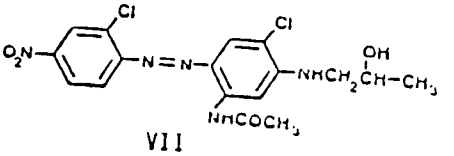

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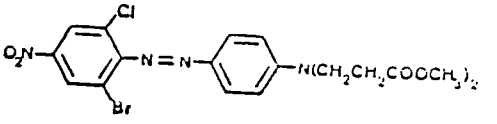

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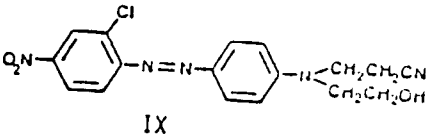

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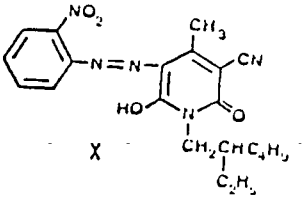

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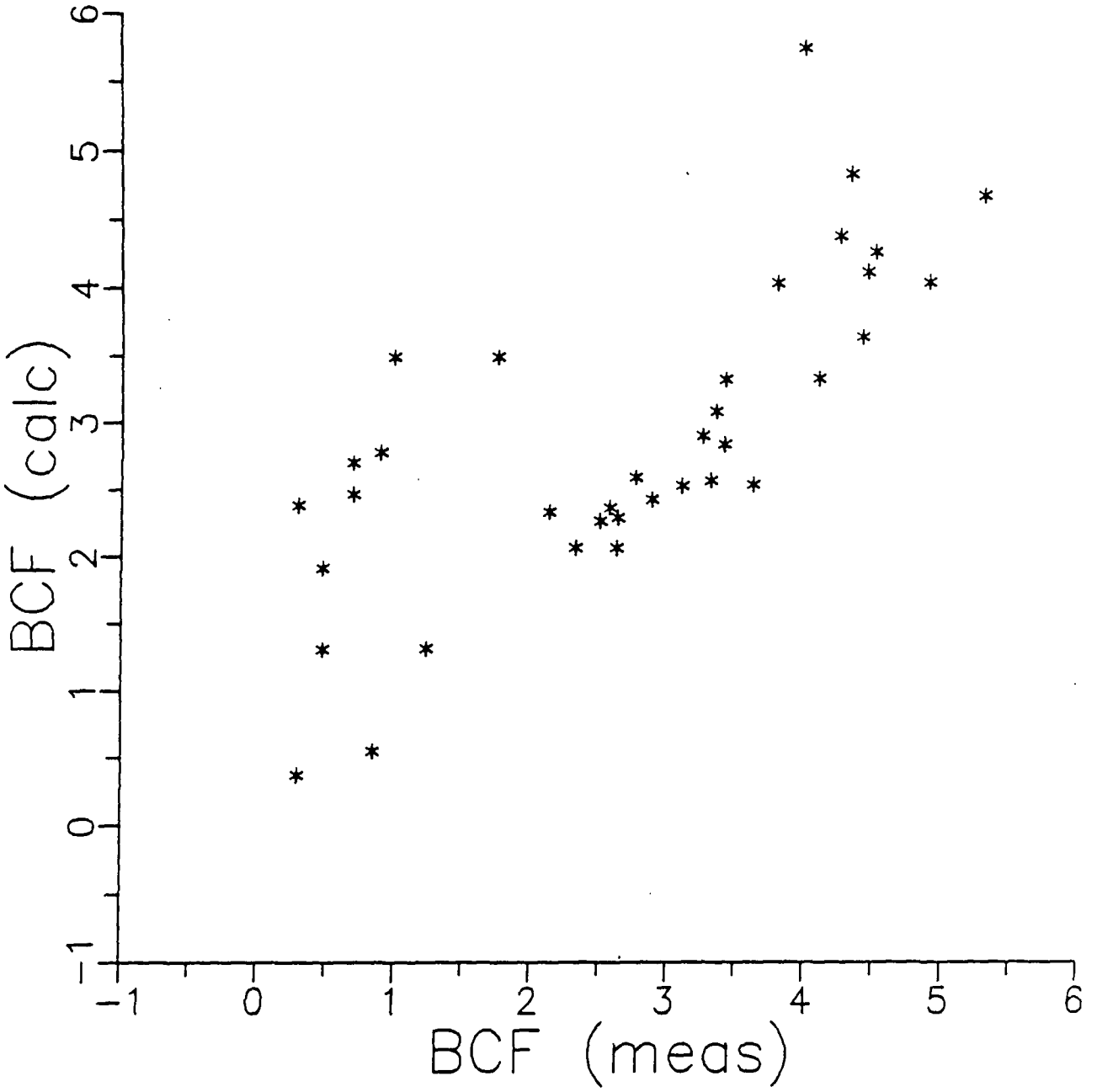

Figure 1. Comparison of measured BCFs with estimates from eq 1.

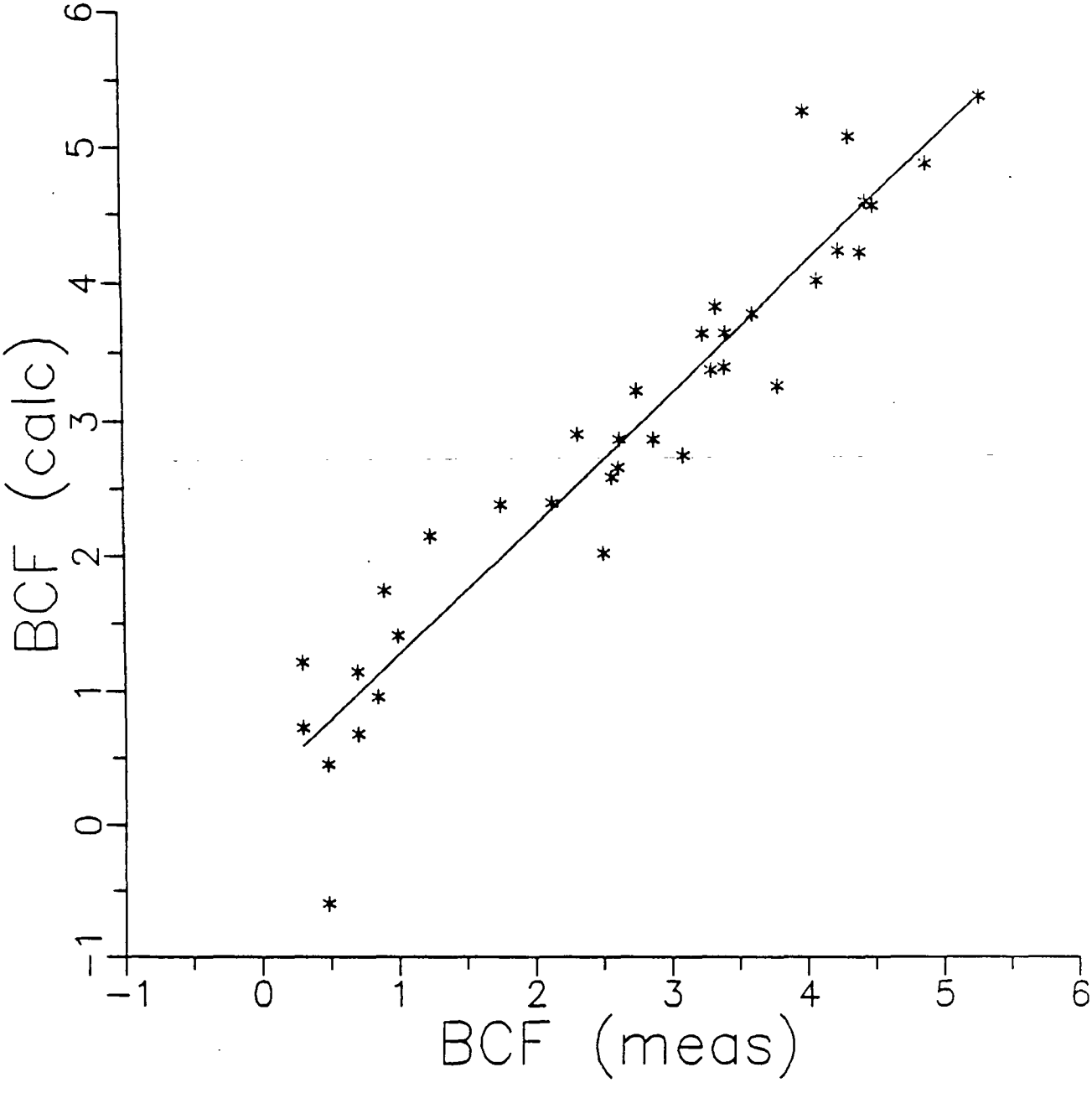

Figure 2. Comparison of measured BCFs with estimates from eq 4.